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Simple/Rapid Test Devices for Anti-HIV Screening: Do They Come Up to the Mark?

Ralph E. Giles, Keith R. Perry, and John V. Parry*

Medical Devices Agency Evaluation Centre, PHLS Hepatitis and Retrovirus Laboratory, Virus Reference Division, Central Public Health Laboratory, London, United Kingdom

Thirteen simple/rapid test devices (S/RTDs) for the detection of antibodies to HIV 1 and HIV 2 were assessed. Ninety-two specimens in four categories were used and results with the thirteen S/RTDs were compared with those obtained with six currently available commercial laboratory-based anti-HIV 1/2 EIAs. Seven of the 13 S/RTDs scored all 26 blood donors' specimens as unreactive, and 11 correctly identified all the 25 "straightforward" anti-HIV positive specimens. False negative results arose when testing by Uni-Gold HIV and SeroCard HIV, which gave 72 and 68 correct positive observations, respectively, out of 75. No S/RTD detected seroconversion earlier than the most sensitive EIAs, but four S/RTDs performed similarly to most of the EIAs. On the low-titre panel specimens, six S/RTDs were less sensitive than the least sensitive EIA and, in contrast to four of the six EIAs, only one S/RTD was able correctly to identify all the positive specimens. A manufacturing problem was identified that allowed the HIV antigen-sensitised area on the membrane of two SeroCard HIV devices to be misaligned with the device's reading window so that the reaction was almost entirely obscured. As long as small numbers of specimens were involved, most S/RTDs required considerably less time and less equipment than EIAs, but overall they were slightly less sensitive. Their use in various health settings and for confirmatory procedures is discussed. ***J. Med. Virol. 59:104–109, 1999.***

KEY WORDS: HIV seroconversion; low titre anti-HIV; sensitivity; specificity; near patient testing; Developing World

INTRODUCTION

Simple/rapid test devices (S/RTDs) have been developed to meet a market demand for rapid small-scale or point of care testing. They might be employed for use in health care settings such as small hospital laboratories, sexually transmitted diseases' clinics, and student health and emergency care centres. Point of care anti-HIV testing kits are covered in the UK by the HIV Testing Kits Services Regulations [1992], which forbid the sale of HIV kits directly to the public. Several S/RTDs have been approved by European regulators though, to date, only one (SUDS HIV 1+2 Test) has been approved by the US Food and Drug Administration (FDA).

In many hospital laboratories, the normal practice is either to batch specimens and test by enzyme immunoassays (EIAs) or by closed automated processors such as AxSym (Abbott Laboratories, Chicago, IL) and VIDAS (bioMérieux Maroy-l'Etoile, France). Most EIAs take 1.5 to 2.0 hours to perform, and they may need sophisticated equipment that requires maintenance, highly trained laboratory staff, access to deionised water, and a reliable electricity supply. A positive reaction by one of these screening methods is then usually investigated by complex and expensive supplementary methods to confirm HIV infection. If sufficiently high positive and negative predictive values could be achieved, anti-HIV S/RTDs might be used singly or in combination, instead of the EIAs, to allow immediate appropriate action while the patient is still at the clinic. In the event of a positive reaction, patients can, at the time of their first consultation, receive suitable counselling, be informed of their likely HIV status, and be asked to return for the results of confirmatory testing. There may be clinical, public health, and financial advantages in early detection and treatment, and reduced loss to follow-up. The use of S/RTDs in hospital and other clinical settings may facilitate HIV-prevention activities.

In the Developing World, the high cost of EIA and Western blot testing, and their requirement for sophisticated equipment, often makes them incompatible

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*Correspondence to: Dr. John V. Parry, Hepatitis & Retrovirus Laboratory, Virus Reference Division, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT.

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with local circumstances. In Africa, field-studies have shown that anti-HIV testing strategies that incorporate S/RTDs may achieve sensitivities and specificities similar to those obtained with EIAs and Western blot. Moreover, some S/RTDs may distinguish between HIV 1 and HIV 2 infections [Kline et al., 1994].

Considering the diversity of S/RTDs marketed currently and under development, and their clinical applications, it is important to identify reliable, specific, and sensitive ones that can be performed quickly and cheaply, with a view to their incorporation into testing strategies. Poor performers may also be identified. Most S/RTDs depend on recombinant DNA technology or oligopeptide synthesis for the production of the HIV 1/HIV 2 antigens employed. They are usually simple to use, often requiring little or no specialist equipment. The end-points are mostly read visually by the operator and the time required to complete each test, or small batches of tests, is usually brief (i.e., a few minutes). Previous evaluations of S/RTDs have only investigated a few devices at a time [Malone et al., 1993; Stetler et al., 1997], and none have used low titre panels as performance indicators. An assessment of the performance of 13 S/RTDs and a comparison with six laboratory-based EIAs follows.

MATERIALS AND METHODS

Specimen Panels

Anti-HIV positive specimens used in this study were drawn from archived samples previously submitted for routine clinical testing and included 22 unremarkable anti-HIV 1 positive specimens from various risk groups as well as three anti-HIV 2 positive specimens. Freshly collected blood donors' sera (n = 26) were obtained from the North London Blood Centre; these were unreactive in the Centre's routine anti-HIV screening test. Two commercial anti-HIV 1 seroconversion panels [PRB927; n = 5, Boston Biomedica, Inc., West Bridgewater, MA (BBI) and 6241; n = 6, Bioclinical Partners, Inc., Franklin, MA (BCP)], each comprising a series of undiluted plasma samples collected from single donors around the time of seroconversion, were also included in the panel. They had previously been shown to discriminate between more and less sensitive EIAs. Two BBI anti-HIV 1 low titre panels (PRB105; n = 15 and PRB106; n = 15) that consisted of undiluted samples obtained from asymptomatic donors selected on the basis of weak reactivity in Western blot, probably reflecting collection shortly after seroconversion, were also included. All samples were stored at −20°C and coded prior to testing so that the evaluators were unaware of the expected results.

Experimental Procedure

Testing was carried out according to each manufacturer's instructions and all results were read visually by three individuals who independently recorded the results using the following criteria: a negative result was scored as "0", an uncertain result was scored as "1", a weak but definite reaction was scored as "2", a medium reaction was scored as "3" and a strong reaction was scored as "4". Specimens giving discordant results were not retested as volumes were limited. Ease of reading of each S/RTD was scored by each of the three evaluators on a scale of 1 (difficult) to 10 (easy).

Analysis of Findings

For the purpose of calculating specificity, indeterminate and positive reactions on anti-HIV negative specimens were both considered to be false. For sensitivity calculations, the absence, or uncertain presence, of reactivity for anti-HIV positive specimens were both considered to be inaccuracies. The individual scores given by each reader were added together allowing a maximum score of 75, 33, and 84 for straightforward anti-HIV positive specimens, seroconversion specimens, and low titre panel specimens, respectively. When comparing S/RTD and conventional EIA results on seroconversion and low titre panel specimens, the number of positive specimens detected by each S/RTD was calculated by taking the majority score given by the three readers. This gave maximum achievable scores of 11 for seroconversion panel specimens and 28 for low titre panel specimens.

Simple/Rapid Test Devices Assessed

Manufacturers/suppliers currently marketing S/RTDs in the UK were invited to submit products for evaluation and to train the evaluators in the use of their product(s). The main features of the thirteen anti-HIV S/RTDs are summarised in Table 1.

RESULTS

Specificity

Six of the thirteen S/RTDs lacked 100% specificity on 26 anti-HIV negative specimens (Table II). Of these six, three gave clear false positive reactivity, with or without ambiguous reactivity with other specimens (Recombigen® HIV-1/HIV-2 RTD, SUDS HIV 1+2 Test and Uni-Gold HIV). The non-specific reactivity of the other three kits (HIVChek™ 1+2 System 3 test Kit, HIV-1&2 Doublecheck™ and SeroCard HIV) was faint and uncertain.

Sensitivity

On the 25 anti-HIV positive specimens two S/RTDs (SeroCard HIV and Uni-Gold HIV) gave falsely negative reactions, leading to sensitivities of 91% and 96%, respectively. In addition, a manufacturing problem was identified in SeroCard HIV. It was observed for two anti-HIV positive specimens that the HIV antigen-sensitised area on the membrane of the SeroCard HIV devices was misaligned with its reading window so that the reaction was almost entirely obscured. Slightly greater misalignment (1–2 mm) or less careful scrutiny of the test window might have given rise to additional false negative findings. Using the scoring system described above, the sensitivity scores on the whole panel ranged from 180 at best (Bionike AQ™ Rapid HIV Test; ranked 1st) to 128 at worst (Sero·Strip HIV-1/HIV-2; ranked 12th). However, very little differ-

TABLE I. Characteristics of the 13 Anti-HIV S/RTDs Evaluated

Assay type and name	Manufacturer/ distributor	Product no.	HIV-1 antigens*	HIV-2 antigens	Volume of specimen required (μL)
Flow-through					
Abbott Testpack™ HIV-1/HIV-2	Abbott Laboratories	1A83-21	Rec. core/env	Rec. env	~1[a]
Bionike AQ™ Rapid HIV Test	Gamidor, Ltd.	GDA200201	Rec. protein, synthetic peptides	Rec. protein, synthetic peptides	50
HIVChek™ 1 + 2 System 3 Test Kit	Ortho Clinical Diagnostics	940647	Rec. gp120, gp41	Env peptides	~50[a]
Multispot HIV-1/ HIV-2	Sanofi-Diagnostics Pasteur	72269	Rec. and peptide gp41	gp36 peptide	~35[a]
Recombigen® HIV-1/ HIV-2 RTD	Cambridge Diagnostics Ireland, Ltd.	96053	Rec. env	Rec. env	20
SUDS HIV 1 + 2 Test	Murex Biotech, Ltd.	VK74/75	p24, gp41 peptides	gp36 peptide	50
Chromatographic					
HIV-1 & 2 Doublecheck™	Orgenics	60332000	Rec. p24, gp41, gp120, biotinylated peptide	Synthetic gp36, biotinylated synthetic	150
SeroCard HIV	Trinity Biotech plc	1200100	gp41 peptide	gp36 peptide	~80[a]
Sero · strip HIV-1/ HIV-2	SDS International, Ltd.	SH-0010	gp41, gp120 synthetic peptides	gp36 synthetic peptide	~1[a]
Uni-Gold™ HIV	Trinity Biotech plc	1206500	gp41, gp120 peptides	gp36 peptide	~50
Agglutination					
Capillus® HIV-1/ HIV-2	Cambridge Diagnostics Ireland, Ltd.	6048G/ 6058G	Rec. env	Rec. env	10
Serodia® · HIV-1/ HIV-2	Fujirebio Inc	9260	Inactivated whole virus particles	Inactivated whole virus particles	25
Dipstick					
Immunocomb® II HIV-1 & 2 BiSpot	Orgenics	60432002	gp41, gp120 peptides	gp36 peptides	50

*rec., recombinant.
[a]Volumes are only approximate since specimens were delivered as 1 drop from a disposable pipette or from a collection loop.

TABLE II. Findings on 13 S/RTDs*

Assay	Specificity[a] (%) (n = 75)	Sensitivity (%) (n = 78)	Ease of reading[b]	End-point stability	Approx. time to complete testing of ten specimens (min)
Capillus® HIV-1/HIV-2	100	100	10	~1.5 hr	33 (digital) 10 (manual)
Abbott Testpack™ HIV-1/HIV-2	100	100	9.3	>24 hr	15
Immunocomb® II HIV-1 & 2 BiSpot	100	100	9	>24 hr	50
Multispot HIV-1/HIV-2	100	100	8.3	>24 hr	22
Bionike AQ™ Rapid HIV Test	100	100	7	~12 hr	6
Serodia® · HIV-1/HIV-2	100	100	7	~2 hr	150
Sero · strip HIV-1/HIV-2	100	100	6	>24 hr	4.5
HIVChek™ 1 + 2 System 3 Test Kit	96	100	9.3	~0.5 hr	6.5
HIV-1 & 2 Doublecheck™	96	100	6.7	~8 hr	21
Recombigen® HIV-1/HIV-2 RTD	92	100	8.3	~4 hr	15
SUDS HIV 1 + 2	92	100	3	~2 hr	17
Uni-Gold™ HIV	88	96	7.3	~1 hr	13
SeroCard HIV	91	91	3.3	2–3 min	14

*Individual tests' performance has been ranked on the basis of the first three columns of results.
[a]See text for an explanation of how results were derived.
[b]Average scores were calculated from scores of the three readers: 1 = very difficult; 10 = very easy.

ence in performance was observed between the eight most sensitive S/RTDs (Table III). The SUDS HIV 1+2 Test was not ranked since it was not possible to determine the point of seroconversion due to non-specific reactivity that occurred when testing several of the specimens. Immunocomb® II HIV-1 & 2 BiSpot, SeroCard HIV, Sero·Strip HIV-1/HIV-2, and Uni-Gold HIV were relatively insensitive.

The highest laboratory-based EIA score for detection of seroconversion was 8 (Genscreen® HIV 1/2 and IMx HIV-1/HIV-2 III Plus) (Table IV), whereas the highest score achieved by any of the S/RTDs was 7 (Bionike

TABLE III. Ranking of S/RTDs According to Overall Sensitivity Findings*

Anti-HIV assay	Aggregate score for anti-HIV positive specimens maximum = 75	Aggregate score for seroconversion panels maximum = 33	Aggregate score for low titre panels maximum = 84	Total score maximum = 192
Bionike AQ™ Rapid HIV Test	75	21	84	180
Recombigen® HIV-1/HIV-2 RTD	75	21	80	176
Serodia® · HIV-1/HIV-2	75	18	80	173
Multispot HIV-1/HIV-2	75	18	77	170
HIVChek™ 1 + 2 System 3 Test Kit	75	16	78	169
Abbott Testpack™ HIV-1/HIV-2	75	15	78	168
HIV-1 & 2 Doublecheck™	75	15	76	166
Capillus® HIV-1/HIV-2	75	15	75	165
Immunocomb® II HIV-1 & 2 BiSpot	75	15	64	154
SeroCard HIV	68	16	55	139
Uni-Gold™ HIV	72	9	50	131
Sero · strip HIV-1/HIV-2	75	6	47	128
SUDS HIV 1 + 2 Test	75	ND	70	NR

*ND, not determined due to inconsistent results. NR, not ranked.

TABLE IV. Ranking of S/RTDs Compared With EIAs and Automated Systems, Based on Results of Seroconversion and Low Titre Panels*

Anti-HIV assay[a]	Product number	Aggregate score[b] for seroconversion panels (PRB927 + 6241) (n = 11)	Aggregate score[b] for low titre panels (PRB105 + 106) (n = 28)
Genscreen® HIV1/2	72277	8[b]	28
IMx HIV-1/HIV-2 III Plus	8C98-20	8	28
Murex HIV 1 + 2 EIA	VK84/85	7	28
Ortho® HIV-1/HIV-2 Ab-capture ELISA	932380	7	28
Bionike AQ™ Rapid HIV Test	**GDA200201**	**7**	**28**
Biotest anti-HIV1/2 recombinant	807005	7	27
Recombigen® HIV-1/HIV-2	**96053**	**7**	**27**
Serodia® · HIV-1/HIV-2	**9260**	**6**	**27**
Abbott TestPack HIV-1/HIV-2	**1A83-21**	**5**	**26**
HIVChek™ 1 + 2 System 3 Test Kit	**940647**	**5**	**26**
Innotest HIV-1/HIV-2	M422	6	25
Multispot HIV-1/HIV-2	**72269**	**6**	**25**
Capillus® HIV-1/HIV-2	**6048G**	**5**	**25**
HIV-1 & 2 Doublecheck™	**60332000**	**5**	**25**
SUDS HIV 1 + 2	**VK74**	**RV**	**23**
Immunocomb® II HIV-1 & 2 BiSpot	**60432002**	**5**	**22**
SeroCard HIV	**1200100**	**5**	**18**
Uni-Gold™ HIV	**1206500**	**3**	**17**
Sero · Strip HIV-1/HIV-2	**SH-0010**	**2**	**16**

*RV, results void.
[a]S/RTDs are shown in bold italics.
[b]The aggregate was calculated by summing the number of positive samples for each of the seroconversion panels. A higher aggregate suggests higher sensitivity.

AQ™ Rapid HIV Test and Recombigen® HIV-1/HIV-2). The equal second most sensitive laboratory-based EIA scored 7, and one achieved a score of 6. By contrast, two of the S/RTDs scored 6, six S/RTDs scored 5, one device scored 3, and one scored 2. None of the S/RTDs was as good at detecting seroconversion as the most sensitive conventional EIAs, though four S/RTDs showed similar sensitivity to most of the EIAs with which their performance was compared. In tests on two low titre panels, four of the EIAs achieved the maximum score of 28, Biotest anti-HIV 1/2 recombinant scored 27, and Innotest HIV-1/HIV-2 scored 25. Only one of the S/RTDs (Bionike AQ™ Rapid HIV Test) was able to achieve the maximum score. The second most sensitive S/RTDs (Recombigen® HIV-1/HIV-2 RTD and Serodia®·HIV-1/2) scored 27, two scored 26, and three scored 25. The remaining five S/RTDs were less sensitive than the least sensitive laboratory-based EIA.

Ease of Reading

The intensity of S/RTD reactions varied between the thirteen S/RTDs. For the "straightforward" anti-HIV positive specimens, one device (Abbott Testpack™ HIV-1/HIV-2) was recorded, in all 75 observations, to give the maximum score of "4" (strong positive reaction). Five other devices gave more than 60 observations of strong positive reactions. These observations further suggest that the sensitivity of the different S/RTDs varies and that some may be more difficult to read. Two devices (SeroCard HIV and SUDS HIV 1+2)

attained an average score of less than 4, indicating that misinterpretation of their results was more likely than for most others (Table II). Four S/RTDs were assigned an ease of reading score greater than 9, one of which (Capillus® HIV-1/HIV-2) achieved the maximum score.

The stability of the end-points (Table II) varies greatly between devices, ranging from 2 to 3 minutes to greater than 24 hours. The end-points for two of the S/RTDs (Immunocomb® II HIV-1&2 BiSpot and Sero strip HIV-1/HIV-2) were stable indefinitely, thus permitting long-term storage of the reactions.

Rapidity of Testing

The time required to complete the testing of ten specimens ranged from 4.5 to 150 minutes (Table II). The timings given are only approximate and, in some cases (those taking longer times), the time needed to test a larger batch of specimens would not increase proportionately with the number of specimens tested. The whole time taken, and the "hands-on" time, depends on the complexity of the procedure. The simplest assays required no more than addition of a small volume of serum to the device and reading of the result, whereas the most complex involved multiple manipulations rather similar to a conventional microplate EIA (Table II).

DISCUSSION

We have demonstrated that the majority of commercially available S/RTDs are not as sensitive as the best conventional EIAs, although most devices were of adequate sensitivity. Of the 13 S/RTDs assessed 11 detected all "straightforward" anti-HIV positive sera. Of the two S/RTDs that gave falsely negative findings on unremarkable anti-HIV positive specimens, one (SeroCard HIV) was found also to have an occasional manufacturing fault that resulted in misalignment of the HIV-reactive area of the membrane and the test viewing window in the outer casing of the device. It was noticed when two anti-HIV positive specimens gave reactions barely visible at the edge of the window. We cannot estimate the frequency of this problem as it may also have been present in SeroCard devices used to test anti-HIV negative specimens, in which it would not have been recognised. Presumably, similar problems could arise in other devices that require careful alignment of reactive areas on a membrane and a viewing window.

The sensitivities of the 11 S/RTDs that detected all unremarkable anti-HIV positive specimens could be differentiated on the basis of challenge by seroconversion and low titre panels. One device (Sero·Strip HIV-1/HIV-2) performed particularly poorly with these panels. Results for other batches of this S/RTD have given more favourable results, suggesting batch-to-batch variability (personal communication, Saliva Diagnostic Systems, Inc., Vancouver, WA). Seroconversion sensitivity of another device (SUDS HIV 1+2 Test) could not be assessed due to non-specific reactivity. Sensitivity results reported for SUDS HIV 1+2 Test on "straightforward" HIV positive specimens have been good [Malone et al., 1993; Carter et al., 1995; Kassler et al., 1995; Stetler et al., 1997], but no results have previously been published on commercial seroconversion panels.

None of the manufacturers' instructions for the S/RTDs suggested that more than one reader was required to interpret the result. Our study showed that ease of reading varied greatly between devices and this was also reflected in occasional differing interpretations between the three readers we employed. Generally, the S/RTDs that scored worse for "ease of reading" were those also with lower sensitivity and specificity, further emphasising the difficulties associated with subjective reading and indistinct assay end-points. Intense positive reactions are the easiest to interpret, and devices that frequently generate weak reaction spots/lines on positive or negative specimens are open to misinterpretation and may therefore lead to misdiagnosis. Cambridge Diagnostics' Capillus HIV-1/HIV-2 gave rise to fewest problems of subjectivity. Nevertheless, Cambridge make available a battery-powered digital reader that interprets the final result. This reader is cheap to buy and use and is well suited to diverse health care settings, including the Developing World.

Because of the relatively small size of the specimen panel, the sensitivity and specificity results presented here provide only a guide to field performance of S/RTDs. To draw firmer conclusions about how each S/RTD performs compared with laboratory-based EIAs larger scale evaluations need to be done. Nevertheless, it seems that most currently available S/RTDs are not as accurate as EIAs and similar automated screening methods. Study of the ability of S/RTDs to detect anti-HIV antibody resulting from infection with various subtypes would provide further information on the value of S/RTDs in settings where non-B subtypes are prevalent [Engelbrecht et al., 1994]. If S/RTDs are to be considered for use in developing countries, HIV type and subtype prevalences, associated specificity and sensitivity, cost-effectiveness, and the operational characteristics of the assays should all be considered. Operationally, although individual S/RTD results may be available rapidly (within minutes), for many of the devices a substantial proportion of the assay time is "hands-on." Consideration needs also to be given to independent result validation by one and preferably two additional personnel. Therefore, S/RTDs may prove efficient only for small-scale testing (up to 12 specimens at a time), and in particular circumstances.

The potential of strategies employing combinations of S/RTDs and laboratory-based EIAs to confirm HIV infection has been extensively investigated [Van der Groen et al., 1991; Behets et al., 1992; Mortimer, 1992; Urassa et al., 1992; Brattegaard et al., 1993; Stetler et al., 1997]. Results have shown that carefully chosen screening assays used in pairs, where the initial assay has the higher sensitivity, often perform at least as well as an initial screening assay supplemented by a

Western blot, the more expensive option. More recent studies have shown that on-site testing with a S/RTD as a screening test in a sexually-transmitted disease clinic resulted in many more patients learning their HIV serostatus, with a saving in overall cost and substantial improvements in the effectiveness of counselling and testing [Kassler et al., 1997; Centres for Disease Control, Update, 1998]. The use of S/RTDs in HIV testing programmes may reduce the need to delay counselling of seronegative patients and provide immediate preliminary results for seropositive patients. This allows rapid access to care and HIV-prevention activities [Irwin et al., 1996], though a reliable S/RTD is essential to its success. Receiving a provisional diagnosis within a few minutes of testing will also secure more patients for confirmatory testing.

This study has demonstrated that a range of performance exists within the group of S/RTDs tested. Two devices were inadequate for most testing regimes. Since this work involved only a limited panel of specimens, the results are only an indication of performance, and a more extensive investigation is required to establish the reliability of all HIV kits of this nature. S/RTDs for anti-HIV, as well as for other viral markers such as HBsAg and anti-HCV, have now begun to flood the market place, making it a matter of urgency to establish their performance characteristics and to determine how they should fit into testing programmes. The absence of requirements for expensive and specialist equipment, and its maintenance, and the potential overall cost savings compared with conventional screening and confirmatory testing, make them particularly suited to use in the Developing World. S/RTDs that offer an accuracy similarly to that of conventional EIAs also strengthen the case for "point-of-care" testing by reducing the turn-around times for results. A combination of S/RTDs may also prove to be as effective as conventional algorithms for screening and confirmation of HIV and other viral infections.

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